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Consolidation treatments after chemoradiotherapy in patients with locally advanced inoperable non-small cell lung cancer: a systematic review and network meta-analysis protocol

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ABSTRACT

Introduction Concurrent chemoradiotherapy (CCRT) is the standard of care for inoperable locally advanced non-small cell lung cancer (LA-NSCLC). To further improve prognosis, the use of consolidation treatments after CCRT has been explored extensively. Although durvalumab is the only consolidation treatment recommended by national clinical practice guidelines, there have been many studies exploring the effectiveness of other agents. However, until now, no studies have compared all agents systematically, and no studies have provided evidence for the optimal combination of different CCRTs and consolidation treatments regimens. This systematic review will evaluate the comparative clinical efficacy of consolidation therapies after CCRT as well as various combinations of CCRTs and consolidation therapies.

Methods and analysis PubMed, the Cochrane Controlled Register of Trials (CENTRAL), EMBASE, and ClinicalTrials.gov will be searched for relevant information. The estimated end date for the search will be February 3, 2022. Each stage of the review, including the study section, data extraction, and risk of bias and quality of evidence assessments, will be performed in duplicate. We will include randomised controlled trials (RCTs) that included participants who received CCRT and consolidation treatment in at least one treatment arm. The primary endpoints will be overall survival and progression-free survival. Tumor response, health-related quality of life, and treatment-related toxicity will be presented as secondary outcomes. Both traditional meta-analysis and network meta-analysis with the Bayesian approach will be conducted. Subgroup analyses and meta-regression will be completed to investigate

heterogeneity, and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination Ethical approval and patient consent are not required as this study is a meta-analysis based on published studies. The results of this study will be submitted to a peer-reviewed journal for publication. In case of any changes in the protocol, protocol amendments will be updated in PROSPERO and explanations of these modifications will be described in the final report of this review. The results of this systematic review and NMA will be published in a peer-reviewed journal.

PROSPERO registration number CRD42021239433.

ARTICLE SUMMARY

Strengths and limitations of this study

- The network meta-analysis (NMA) will compare the effectiveness of various consolidation treatments with/without concurrent chemoradiotherapies (CCRTs) for patients with inoperable locally advanced non-small cell lung cancer (LA-NSCLC) through a Bayesian method.
- For the first time the efficacy and safety of all the randomized controlled trials (RCTs) whether they randomized consolidation treatments only to patients not progressing after CCRT or randomized patients at onset of CCRT will be comprehensively assessed in a NMA.
- We will use global and local methods to evaluate consistency, subgroup analyses and meta-regression to explore heterogeneity, sensitivity analyses to ensure the stability of results and the Grades of Recommendation, Assessment, Development and Evaluation approach

to evaluate the quality of evidence.

INTRODUCTION

Lung cancer is still a worldwide epidemic. It is estimated that approximately 235,760 new cases of lung cancer were diagnosed in the United States in 2021, and there were 131,880 deaths.[1] Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases, and about one third of NSCLC patients are diagnosed at the locally advanced stage.[2] Locally advanced NSCLC (LA-NSCLC) represents a complex and heterogeneous group of patients and includes several clinically distinct sub-stages that do not have a single, widely accepted standard of care.[3] The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC define locally advanced disease as stages II and III with positive nodes (N+).[4] For patients with inoperable LA- NSCLC, a combined modality approach with radiotherapy and chemotherapy is one standard of care consideration that can improve survival times compared with radiotherapy alone.[5-9] Additionally, several randomized clinical trials and meta-analyses have generally demonstrated that concurrent treatment significantly prolongs survival in comparison with the sequential approach.[10-13] Although concurrent chemoradiotherapy (CCRT) is considered standard care, the prognosis of LA-NSCLC remains poor, with a 5-year survival rate of approximately 13% to 36% at best, and many important questions have not been resolved.[14-16] Moreover, the optimal concurrent chemotherapy and radiotherapy regimens have not been determined. In addition, even with CCRT, patients with locally advanced disease have high rates of relapse and a high frequency of sub-clinical micrometastases.[17] To

decrease the incidence of distant metastasis, consolidation chemotherapy (CCT) (defined as continuation of chemotherapy after completion of CCRT, in a patient whose tumor had been controlled) after CCRT was tried.[17-18] Nevertheless, the data now available on the effectiveness of CCT is still inconclusive. According to the results of a meta-analysis, CCT improved overall survival (OS) (pooled HR 0.85; 95% CI 0.73–0.99; P = 0.03) but did not improve progression-free survival (PFS) (pooled HR 0.78; 95% CI 0.60–1.02; P = 0.07) or overall response rate (ORR) (P = 0.26). However, this research also included retrospective trials and only included five studies in total. Moderate heterogeneity was found in the meta-analysis of OS (I^2 = 51%, P = 0.09). As a consequence, conclusions about the effectiveness of CCT after CCRT remain unclear based on the results of the meta-analysis.[19] In addition, along with the introduction of targeted therapy, there is increasing interest in studying the effectiveness of this class of agents as consolidation therapies, but the results of several clinical trials have been discouraging.[17, 20-21] Understanding the molecular mechanisms associated with tumor immunology and the role of immune checkpoints in the suppression of the antitumor immune response has increased dramatically since 2010.[18] Based on the evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells, which is a predictive factor for a response to PD-1/PD-L1 antibodies, the PACIFIC protocol was designed.[22-27] PACIFIC demonstrated the effectiveness of using the anti-PD-L1 agent durvalumab as consolidation therapy after CCRT for the treatment of unresectable LA-NSCLC.[27] The success of consolidation immunotherapy in the PACIFIC study changed the treatment paradigm for unresectable stage III NSCLC, and other agents are also under investigation.[4, 17] Overall, there have been a number of studies exploring the clinical effects of different

consolidation treatments in order to further improve prognosis. Moreover, some studies gave randomized consolidation treatments only to those patients who did not progress after CCRT, and other trials have, in contrast, randomized patients at the onset of CCRT. The first case is suitable for examining the effects of consolidation therapies, but the second case is more suitable when investigating the optimal CCRT in combination with consolidation treatment. However, until now, there have been no studies that collected and analyzed all the evidence systematically. Traditional meta-analyses can only perform pairwise direct comparisons of treatments, whereas network meta-analysis (NMA) can compare three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies.[28] NMA is also able to provide the ranking of treatment options based on their effectiveness. Therefore, to help clinicians and patients understand the status of CCRT and consolidation treatment research and make better choices, a systematic review and NMA should be conducted to summarize the evidence on various therapies and identify the most effective consolidation treatment and optimal combination of CCRT and consolidation therapy.

OBJECTIVES

To assess the effectiveness and toxicity of different consolidation treatments with/without CCRTs for patients with inoperable LA- NSCLC.

To rank different consolidation treatments with/without CCRTs based on their efficacy and tolerability using a network meta-analysis.

METHODS

This protocol will be reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P), and this network meta-analysis will be conducted

and reported in accordance with PRISMA extension version (PRISMA-NMA).[29-30]

Inclusion criteria

Types of studies

We will only include randomized controlled trials (RCTs). We will include both full-text and abstract publications if sufficient information on study design, characteristics of participants (patients with inoperable LA-NSCLC), and interventions (CCRT and consolidation treatment) are provided. We will include trials that included participants who received CCRT and consolidation treatments in at least one treatment arm. We will not include quasi-RCTs.

Types of participants

Adult participants (aged ≥18 years) with histologically or cytologically confirmed LA-NSCLC (stages II and III with positive nodes) will be included. People should have no history of radiation therapy (including brachytherapy) or systematic treatments (including chemotherapy or immunotherapy) before CCRT. Patients should be medically inoperable or refuse surgery and not be selected for driver genes.

Types of interventions

Any combination of CCRT (can also be concurrent radiotherapy and targeted therapy or immunotherapy, etc.) and consolidation therapy (including chemotherapy, immunotherapy, molecularly targeted agents, etc.) will be included. Consolidation therapy is given to non-progressing patients after CCRT. Studies in which randomization was performed before CCRT or only on patients with no disease progression after CCRT will be included.

Outcome measurements

a) *Primary outcomes*

Overall survival (OS): defined as the time from randomization until death from any cause.

Progression-free survival (PFS): defined as the time from randomization to any progression or death.

b) Secondary outcomes

Tumor response to treatment (including complete response, partial response, progressive disease or stable disease): response to treatment defined according to RECIST guidelines.[31]

Health related quality of life (HRQoL): measured by a validated scale (e.g. EORTC QLQ-C30).[32]

Treatment related toxicity: Grade ≥ 3 treatment related adverse events will be our main concerns because they are more meaningful for clinicians. The treatment related adverse events can be defined according to the criteria of CTCAE (Common Toxicity Criteria for Adverse Events) or by the authors of the included studies if it is reasonable.[33]

RCTs will be excluded according to the following criteria: (1) surgery or induction chemotherapy was offered in addition to CCRT and (2) studies in which consolidation therapy was optional for patients .

Electronic search

We will search the following databases and resources:

•The Cochrane Central Register of Controlled Trials (CENTRAL; latest issue);

•MEDLINE accessed via PubMed (1946 to present);

•Embase (1980 to present);

•The WHO International Clinical Trials Registry Platform (ICTRP) search portal (https://apps.who.int/trialsearch/AdvSearch.aspx) for all prospectively registered and ongoing trials;

•ClinicalTrials.gov (https://www.clinicaltrials.gov/)

There will be no limitations on language of publication, year of publication, or publication status. Available references from relevant reviews will be hand-searched to find additional studies. We will use the search strategies developed by YZ and reviewed by an experienced librarian researcher (JH-T). We will search all databases using the combination of controlled vocabulary (e.g. medical subject headings (MeSH) in MEDLINE, Emtree in Embase) and free-text terms. Our PubMed complete search strategy is presented in online supplemental file 1 (see the online supplemental appendix 1). The retrieved records will be managed by EndNote V.X9 (Clarivate Analytics, Philadelphia, Pennsylvania, USA), and the search results will be recorded in a pre-defined Excel sheet.

Study selection

Firstly, duplicate studies will be excluded from the retrieved records using the "find duplicate" function in EndNote V.X9 software. Then, two reviewers (YZ, H-M F) will screen the titles and abstracts independently and select the remaining articles that meet the predefined inclusion criteria for full-text evaluation. After browsing the full texts, studies that satisfy the inclusion criteria will be finally reviewed. Studies that include relevant data for synthesis of effect estimates will be included in the NMA. We will record the reasons for excluding the full texts and generate a PRISMA flow diagram for the NMA (Figure 1).[34] When multiple publications

of the same study are present, the data for the longest follow-up period will be used. All discrepancies will be solved by consensus and if necessary we will consult a third review author (J-H T). The authors will be contacted if more information is required to determine eligibility for inclusion.

Figure 1 Flow diagram of study selection process

Data extraction and management

Two independent reviewers (YZ, H-M F) will extract data from the included RCTs and input them into a pre-designed electronic data extraction form. We will extract the following information from the eligible primary studies: Publication details (i.e., publication year, country, authors, affiliation of authors, single-center or multicenter, total sample size, funding source); study methodology (setting, study design, method of randomization, allocation concealment, blinding, total duration of study, duration of follow-up period, and withdrawals, method of statistical analysis [intention-to-treat analysis or per-protocol analysis], and year trial started); participants (sample size, numbers enrolled in each arm, mean age, age range, gender, Eastern Cooperative Oncology Group (ECOG) performance status, diagnostic criteria, NSCLC histological subtype, staging of NSCLC, staging system used, inclusion and exclusion criteria, smoking history, PD-L1 status, driver genes status); intervention (details of CCRT regimens, type of radiotherapy, radiotherapy regimen, and details of consolidation treatment); and outcome measures (primary and secondary results, reported time points, type of questionnaires used to assess HRQoL). For dichotomous data (i.e., tumor response, treatment related adverse effects), the number of participants and the number of participants experiencing the event in

each intervention group will be extracted. For continuous data (e.g., health-related quality of life measures), the number of participants and the mean and standard deviation/standard error for each intervention group will be extracted. For survival outcomes, we will extract hazard ratios (HRs) with corresponding 95% credible intervals (CIs). When HRs and/or 95% CIs are not reported, we will calculate them according to the method described by Tierney and colleagues.[35] When both the observed results and adjusted results are reported, the observed results will be extracted. If only the adjusted results are available, the adjusted results will be extracted, and they will be specified as the adjusted estimates.[36] If the data is presented only in graphs, we will use software such as the GetData Graph Digitizer (http://www.getdata-graph-digitizer.com/) or similar software to extract data. Any disagreement will be resolved by discussion.

Bias risk

The risk of bias of included RCTs will be evaluated according to 'Risk of bias' tool outlined in the Cochrane handbook, which include the following domains: random sequence generation (per study), allocation concealment (per study), blinding of participants and personnel (per outcome), blinding of outcome assessment (per outcome), incomplete outcome data (per outcome), selective reporting and other bias (per study). We will classify each domain as 'low', 'high' or 'uncertain' risk of bias for each included study.[37] Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer (J-H T) if needed.

Quality of evidence

Two authors (YZ and H-M F) will independently evaluate and present the quality of the evidence for each outcome using Grades of Recommendation, Assessment, Development and

Evaluation (GRADE), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias.[38-39] Quality of evidence can be graded into four levels: high, moderate, low, and very low quality. The initial confidence level for each RCT will be set as high but will be rated down based on evaluations of the five domains. If there are any disagreements, we will consult a third author (J-H T). We will follow the approach suggested by Brignardello and colleagues to evaluate confidence in evidence from a network meta-analysis.[40-42]

Data synthesis

The assumption of transitivity and geometry of the networks

Considering the transitivity and homogeneity, we will divide all the evidence included into two categories. The RCTs that randomized patients at onset of CCRT will be analyzed in an NMA (Category 1), and the RCTs that randomized consolidation treatments only to patients who did not progress after CCRT will be combined and analyzed in another NMA (Category 2). We will assess transitivity by comparing the distribution of the effect modifiers across the different comparisons. All information regarding patient and study characteristics will be presented. A network plot will be generated using STATA 14.2 (Stata Corporation, College Station, USA) to present the geometry of the network of treatment comparisons across trials and assess the feasibility of the NMA. If any trials are not connected with the network plot consisting of other trials, these will be excluded from NMA, and the results of these trials will just be described. Nodes will indicate the different consolidation treatments with/without CCRTs included in this review. The size of the nodes and thickness of the edges will be related to sample sizes of interventions and number of included trials, respectively.[43-44]

Statistical analysis

For each outcome, we will calculate the summary estimates of treatment effects with 95% CIs. For dichotomous data (i.e., tumor response, adverse effects), we will use the risk ratios (RRs) or odds ratios (ORs). For continuous data (i.e., HRQoL), we will calculate the mean differences (MDs) if outcome measurements in all studies are made on the same scale. When studies used different scales, we will use the standardized mean differences (SMDs). For time-to-event variables (i.e., OS, PFS), we will use HRs. For direct comparisons, we will use Review Manager 5.4 (Review Manager 2020, the Nordic Cochrane Center, the Cochrane Collaboration) to calculate the intervention effect. For NMA, a Bayesian NMA using the Markov chain Monte Carlo method will be performed using WinBUGS V.1.4.3 (MRC Biostatistics Unit, Cambridge, UK). We will use a hierarchical Bayesian model using three different initial values and will set 100,000 iterations after a burn-in of 50,000 for each chain. We will use the Brooks-Gelman-Rubin plots method to assess the model convergence.[45] We will set vague or flat priors, N(0, 100^2), for trials baselines and treatment effect priors. We will run both random-effects model and fixed-effects model according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents.[46] We will select the model with the lower value of deviance information criterion (DIC) and the value of residual deviance which is closer to data points to explain our results. We will calculate the probability of each treatment at each possible rank and estimate the surface under the cumulative ranking curve (SUCRA).[47] We will assess inconsistency between direct and indirect sources of evidence. We will fit both inconsistency model and consistency model. We will also complete node splitting method to explore local inconsistency.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the important clinical characteristics and methodological differences of included trials. Statistical heterogeneity will be assessed by P value (< 0.10) from the Chi^2 test and the I^2 index. We will consider the P value < 0.10, and/or the value of I^2 statistic > 50% to indicate substantial statistical heterogeneity. Heterogeneity parameter τ derived from the network meta-analysis can also be used to evaluate heterogeneity. For direct comparisons, if there is no heterogeneity, a fixed-effects model will be used for meta-analysis; otherwise, a random-effects model will be adopted.

Dealing with missing data

If important data are not reported, we will make efforts to contact the study authors to obtain detailed information. We will use intention-to-treat (ITT) data whenever possible. Otherwise, we will use the data available to us, but the potential impact of them will be addressed in the assessment of risk of bias. If we cannot get the reply from authors, the data will be verified from other trials in the network or from other published meta-analyses.[48-49]

Measures for publication bias

Publication bias will be examined with the funnel plot method if at least 10 studies are included for any outcome. Small-study effects for the NMA will be assessed by constructing a comparison-adjusted funnel plot taking into account different comparisons. In the absence of small study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.[50]

Subgroup analyses and sensitivity analyses

We will perform subgroup analyses. Besides, we will also complete network meta-regression to explore statistical heterogeneity across trials and inconsistency if at least 10 studies are included. We will focus on following possible effect modifiers: histology; stage of disease; expression of PD-L1; types and statuses of driver genes; risk of bias; doses and regimens of radiotherapy. We will execute sensitivity analyses to examine the robustness of the review findings through excluding unpublished studies, excluding lower quality studies and comparing the results of the random-effects model and the fixed-effect model.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

CCRT is a superior option and the standard care for inoperable LA- NSCLC compared with radiotherapy alone and sequential chemoradiotherapy. Consolidation therapy is a further attempt to control distant metastasis, but there are no conclusive answers yet about the effectiveness of this approach. In addition, with advances in technology, new agents (such as molecular-targeted therapy and immunotherapy) provide more treatment options. Although using durvalumab as consolidation therapy after CCRT for the treatment of unresectable LA-NSCLC is recommended in the NCCN guidelines, no studies have compared the effectiveness of all types of consolidation therapy. In addition, different CCRT regimens are used, and whether an optimal combination of CCRT and consolidation treatment exists is inconclusive. We designed this systematic review and NMA to evaluate the effects of different consolidation treatments with or without CCRTs for LA-NSCLC by synthesizing all current evidence. This

NMA will combine both direct and indirect evidence via a thorough search strategy, prespecified data extraction form, and statistical methods with a Bayesian approach. The result of this NMA will provide valuable information on inoperable LA-NSCLC therapeutic options for clinicians and health practitioners.

Contributors Y-Z, JH-T participated in the conception and design of the study, including search strategy development. YZ, HM-F, QY, and KH-Y tested the feasibility of the study. Y-Z, HM-F wrote the manuscript. YZ, LG, JH-T participated in the methodology. All the authors critically reviewed this manuscript and approved the final version.

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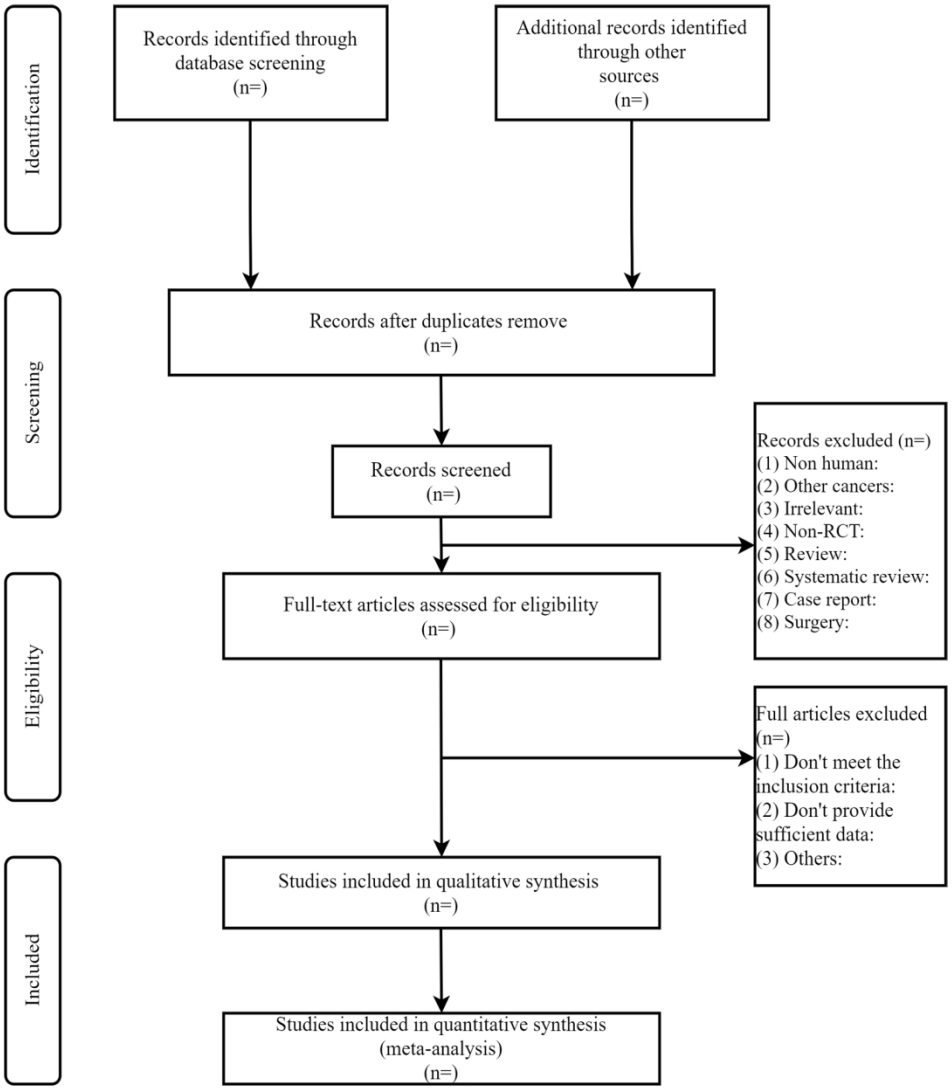

Figure 1. Flow diagram of study selection process

Medline search strategy:

Search	Query
#1	"Lung Neoplasms"[MeSH Terms]
#2	"carcinoma, non small cell lung"[MeSH Terms]
#3	(((((((NSCLC[Title/Abstract]) OR (lung cancer*[Title/Abstract])) OR (lung carcinom*[Title/Abstract])) OR (lung neoplasm*[Title/Abstract])) OR (lung tumor*[Title/Abstract])) OR (lung tumour*[Title/Abstract])) OR (non small cell*[Title/Abstract])) OR (nonsmall cell*[Title/Abstract])
#4	#1 OR #2 OR #3
#5	"Chemoradiotherapy"[MeSH Terms]
#6	((chemoradiotherap*[Title/Abstract]) OR (radiochemotherap*[Title/Abstract])) OR (CCRT[Title/Abstract])
#7	#5 OR #6
#8	"Radiotherapy"[MeSH Terms]
#9	((radiotherap*[Title/Abstract]) OR (radiation therap*[Title/Abstract])) OR (radiation treatment*[Title/Abstract])
#10	#8 OR #9
#11	("Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Antineoplastic Agents"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Induction Chemotherapy"[Mesh]) OR "Combined Modality Therapy"[Mesh]
#12	"chemotherap*"[Title/Abstract]
#13	#11 OR #12
#14	#10 AND #13
#15	#7 OR #14
#16	"Consolidation Chemotherapy"[MeSH Terms]
#17	"Maintenance Chemotherapy"[MeSH Terms]
#18	((((prolonged[Title/Abstract]) OR (duration[Title/Abstract])) OR (continu*[Title/Abstract])) OR (consolidation[Title/Abstract])) OR (maintenance[Title/Abstract])
#19	#16 OR #17 OR #18
#20	"Randomized Controlled Trial"[Publication Type]
#21	((((randomized[Title/Abstract]) OR (placebo[Title/Abstract])) OR (random*[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])
#22	#20 OR #21
#23	#4 AND #15 AND #19 AND #22

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A It is a new study
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A No funder
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A No funder
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-9
Information	#9	Describe all intended information sources (such as electronic	8-9

sources		databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9 supplemental file 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the	11

		outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-14
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11-12

BMJ Open

Consolidation treatments after chemoradiotherapy in patients with locally advanced inoperable non-small cell lung cancer: a systematic review and network meta-analysis protocol

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Consolidation treatments after chemoradiotherapy in patients with locally advanced inoperable non-small cell lung cancer: a systematic review and network meta-analysis protocol

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KEYWORDS non-small cell lung cancer; concurrent chemoradiotherapy; consolidation treatments; network meta-analysis; protocol

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ABSTRACT

Introduction Concurrent chemoradiotherapy (CCRT) is the standard of care for inoperable locally advanced non-small cell lung cancer (LA-NSCLC). To further improve prognosis, the use of consolidation treatments after CCRT has been explored extensively. Although durvalumab is the only consolidation treatment recommended by national clinical practice guidelines, there have been many studies exploring the effectiveness of other agents. However, until now, no studies have compared all agents systematically, and no studies have provided evidence for the optimal combination of different CCRTs and consolidation treatments regimens. This systematic review will evaluate the comparative clinical efficacy of consolidation therapies after CCRT as well as various combinations of CCRTs and consolidation therapies.

Methods and analysis PubMed, the Cochrane Controlled Register of Trials (CENTRAL), EMBASE, and ClinicalTrials.gov will be searched for relevant information. The estimated end date for the search will be February 3, 2022. Each stage of the review, including the study section, data extraction, and risk of bias and quality of evidence assessments, will be performed in duplicate. We will include randomised controlled trials (RCTs) that included participants who received CCRT and consolidation treatment in at least one treatment arm. The primary endpoints will be overall survival and progression-free survival. Tumor response, health-related quality of life, disease-free survival and treatment-related toxicity will be presented as secondary outcomes. Both traditional meta-analysis and network meta-analysis with the Bayesian approach will be conducted. Subgroup analyses and meta-regression will be

completed to investigate heterogeneity, and sensitivity analyses will be conducted to assess the robustness of the findings.

Ethics and dissemination Ethical approval and patient consent are not required as this study is a meta-analysis based on published studies. The results of this study will be submitted to a peer-reviewed journal for publication. In case of any changes in the protocol, protocol amendments will be updated in PROSPERO and explanations of these modifications will be described in the final report of this review. The results of this systematic review and NMA will be published in a peer-reviewed journal.

PROSPERO registration number CRD42021239433.

ARTICLE SUMMARY

Strengths and limitations of this study

- The network meta-analysis (NMA) will compare the effectiveness of various consolidation treatments with/without concurrent chemoradiotherapies (CCRTs) for patients with inoperable locally advanced non-small cell lung cancer (LA-NSCLC) through a Bayesian method.
- For the first time the efficacy and safety of all the randomized controlled trials (RCTs) whether they randomized consolidation treatments only to patients not progressing after CCRT or randomized patients at onset of CCRT will be comprehensively assessed in a NMA.
- We will use global and local methods to evaluate consistency, subgroup analyses and meta-regression to explore heterogeneity, sensitivity analyses to ensure the stability of results

and the Grades of Recommendation, Assessment, Development and Evaluation approach to evaluate the quality of evidence.

INTRODUCTION

Lung cancer is still a worldwide epidemic. It is estimated that approximately 235,760 new cases of lung cancer were diagnosed in the United States in 2021, and there were 131,880 deaths.[1] Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases, and about one third of NSCLC patients are diagnosed at the locally advanced stage.[2] Locally advanced NSCLC (LA-NSCLC) represents a complex and heterogeneous group of patients and includes several clinically distinct sub-stages that do not have a single, widely accepted standard of care.[3] The National Comprehensive Cancer Network (NCCN) guidelines for NSCLC define locally advanced disease as stages II and III with positive nodes (N+).[4] For patients with inoperable LA-NSCLC, a combined modality approach with radiotherapy and chemotherapy is one standard of care consideration that can improve survival times compared with radiotherapy alone.[5-9] Additionally, several randomized clinical trials and meta-analyses have generally demonstrated that concurrent treatment significantly prolongs survival in comparison with the sequential approach.[10-13] Although concurrent chemoradiotherapy (CCRT) is considered standard care, the prognosis of LA-NSCLC remains poor, with a 5-year survival rate of approximately 13% to 36% at best, and many important questions have not been resolved.[14-16] Moreover, the optimal concurrent chemotherapy and radiotherapy regimens have not been determined. In addition, even with CCRT, patients with locally advanced disease

have high rates of relapse and a high frequency of sub-clinical micrometastases.[17] To decrease the incidence of distant metastasis, consolidation chemotherapy (CCT) (defined as continuation of chemotherapy after completion of CCRT, in a patient whose tumor had been controlled) after CCRT was tried.[17-18] Nevertheless, the data now available on the effectiveness of CCT is still inconclusive. According to the results of a meta-analysis, CCT improved overall survival (OS) (pooled HR 0.85; 95% CI 0.73–0.99; P = 0.03) but did not improve progression-free survival (PFS) (pooled HR 0.78; 95% CI 0.60–1.02; P = 0.07) or overall response rate (ORR) (P = 0.26). However, this research also included retrospective trials and only included five studies in total. Moderate heterogeneity was found in the meta-analysis of OS (I^2 = 51%, P = 0.09). As a consequence, conclusions about the effectiveness of CCT after CCRT remain unclear based on the results of the meta-analysis.[19] In addition, along with the introduction of targeted therapy, there is increasing interest in studying the effectiveness of this class of agents as consolidation therapies, but the results of several clinical trials have been discouraging.[17, 20-21] Understanding the molecular mechanisms associated with tumor immunology and the role of immune checkpoints in the suppression of the antitumor immune response has increased dramatically since 2010.[18] Based on the evidence suggesting that chemotherapy and radiotherapy may up-regulate PD-L1 expression on tumor cells, which is a predictive factor for a response to PD-1/PD-L1 antibodies, the PACIFIC protocol was designed.[22-27] PACIFIC demonstrated the effectiveness of using the anti-PD-L1 agent durvalumab as consolidation therapy after CCRT for the treatment of unresectable LA-NSCLC.[27] The success of consolidation immunotherapy in the PACIFIC study changed the treatment paradigm for unresectable stage III NSCLC, and other agents are also under investigation.[4,

17] Overall, there have been a number of studies exploring the clinical effects of different consolidation treatments in order to further improve prognosis. Moreover, some studies gave randomized consolidation treatments only to those patients who did not progress after CCRT, and other trials have, in contrast, randomized patients at the onset of CCRT. The first case is suitable for examining the effects of consolidation therapies, but the second case is more suitable when investigating the optimal CCRT in combination with consolidation treatment. However, until now, there have been no studies that collected and analyzed all the evidence systematically. Traditional meta-analyses can only perform pairwise direct comparisons of treatments, whereas network meta-analysis (NMA) can compare three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies.[28] NMA is also able to provide the ranking of treatment options based on their effectiveness. Therefore, to help clinicians and patients understand the status of CCRT and consolidation treatment research and make better choices, a systematic review and NMA should be conducted to summarize the evidence on various therapies and identify the most effective consolidation treatment and optimal combination of CCRT and consolidation therapy.

OBJECTIVES

To assess the effectiveness and toxicity of different consolidation treatments with/without CCRTs for patients with inoperable LA- NSCLC.

To rank different consolidation treatments with/without CCRTs based on their efficacy and tolerability using a network meta-analysis.

METHODS

This protocol will be reported according to the preferred reporting items for systematic review

and meta-analysis protocols (PRISMA-P), and this network meta-analysis will be conducted and reported in accordance with PRISMA extension version (PRISMA-NMA).[29-30]

Inclusion criteria

Types of studies

We will only include randomized controlled trials (RCTs). We will include both full-text and abstract publications if sufficient information on study design, characteristics of participants (patients with inoperable LA-NSCLC), and interventions (CCRT and consolidation treatment) are provided. We will include trials that included participants who received CCRT and consolidation treatments in at least one treatment arm. We will not include quasi-RCTs.

Types of participants

Adult participants (aged ≥18 years) with histologically or cytologically confirmed LA-NSCLC (stages II and III with positive nodes) will be included. People should have no history of radiation therapy (including brachytherapy) or systematic treatments (including chemotherapy or immunotherapy) before CCRT. Patients should be medically inoperable or refuse surgery and not be selected for driver genes.

Types of interventions

Any combination of CCRT (can also be concurrent radiotherapy and targeted therapy or immunotherapy, etc.) and consolidation therapy (including chemotherapy, immunotherapy, molecularly targeted agents, etc.) will be included. Consolidation therapy is given to non-progressing patients after CCRT. Studies in which randomization was performed before CCRT or only on patients with no disease progression after CCRT will be included.

Outcome measurements

a) *Primary outcomes*

Overall survival (OS): defined as the time from randomization until death from any cause.

Progression-free survival (PFS): defined as the time from randomization to any progression or death.

b) *Secondary outcomes*

Disease-free survival (DFS): defined as the time from randomization to the date of the first recorded evidence of clinical (local or regional) recurrence and/or distant metastasis, as confirmed with imaging, histologic evidence, or death from any cause.

Tumor response to treatment (including complete response, partial response, progressive disease or stable disease): response to treatment defined according to RECIST guidelines.[31]

Health related quality of life (HRQoL): measured by a validated scale (e.g. EORTC QLQ-C30).[32]

Treatment related toxicity: Grade ≥ 3 treatment related adverse events will be our main concerns because they are more meaningful for clinicians. The treatment related adverse events can be defined according to the criteria of CTCAE (Common Toxicity Criteria for Adverse Events) or by the authors of the included studies if it is reasonable.[33]

RCTs will be excluded according to the following criteria: (1) surgery or induction chemotherapy was offered in addition to CCRT and (2) studies in which consolidation therapy

was optional for patients.

Electronic search

We will search the following databases and resources:

•The Cochrane Central Register of Controlled Trials (CENTRAL; latest issue);

•MEDLINE accessed via PubMed (1946 to present);

•Embase (1980 to present);

•The WHO International Clinical Trials Registry Platform (ICTRP) search portal (https://apps.who.int/trialsearch/AdvSearch.aspx) for all prospectively registered and ongoing trials;

•ClinicalTrials.gov (https://www.clinicaltrials.gov/)

There will be no limitations on language of publication, year of publication, or publication status. Available references from relevant reviews will be hand-searched to find additional studies. We will use the search strategies developed by YZ and reviewed by an experienced librarian researcher (JH-T). We will search all databases using the combination of controlled vocabulary (e.g. medical subject headings (MeSH) in MEDLINE, Emtree in Embase) and free-text terms. Our PubMed complete search strategy is presented in online supplemental file 1 (see the online supplemental appendix 1). The retrieved records will be managed by EndNote V.X9 (Clarivate Analytics, Philadelphia, Pennsylvania, USA), and the search results will be recorded in a pre-defined Excel sheet.

Study selection

Firstly, duplicate studies will be excluded from the retrieved records using the "find duplicate" function in EndNote V.X9 software. Then, two reviewers (YZ, H-M F) will screen the titles

and abstracts independently and select the remaining articles that meet the predefined inclusion criteria for full-text evaluation. After browsing the full texts, studies that satisfy the inclusion criteria will be finally reviewed. Studies that include relevant data for synthesis of effect estimates will be included in the NMA. We will record the reasons for excluding the full texts and generate a PRISMA flow diagram for the NMA (Figure 1).[34] When multiple publications of the same study are present, the data for the longest follow-up period will be used. All discrepancies will be solved by consensus and if necessary we will consult a third review author (J-H T). The authors will be contacted if more information is required to determine eligibility for inclusion.

Figure 1 Flow diagram of study selection process

Data extraction and management

Two independent reviewers (YZ, H-M F) will extract data from the included RCTs and input them into a pre-designed electronic data extraction form. We will extract the following information from the eligible primary studies: Publication details (i.e., publication year, country, authors, affiliation of authors, single-center or multicenter, total sample size, funding source); study methodology (setting, study design, method of randomization, allocation concealment, blinding, total duration of study, duration of follow-up period, and withdrawals, method of statistical analysis [intention-to-treat analysis or per-protocol analysis], and year trial started); participants (sample size, numbers enrolled in each arm, mean age, age range, gender, Eastern Cooperative Oncology Group (ECOG) performance status, diagnostic criteria, NSCLC histological subtype, staging of NSCLC, staging system used, inclusion and exclusion criteria,

smoking history, PD-L1 status, driver genes status); intervention (details of CCRT regimens, type of radiotherapy, radiotherapy regimen, and details of consolidation treatment); and outcome measures (primary and secondary results, reported time points, type of questionnaires used to assess HRQoL). For dichotomous data (i.e., tumor response, treatment related adverse effects), the number of participants and the number of participants experiencing the event in each intervention group will be extracted. For continuous data (e.g., health-related quality of life measures), the number of participants and the mean and standard deviation/standard error for each intervention group will be extracted. For survival outcomes, we will extract hazard ratios (HRs) with corresponding 95% credible intervals (CIs). When HRs and/or 95% CIs are not reported, we will calculate them according to the method described by Tierney and colleagues.[35] When both the observed results and adjusted results are reported, the observed results will be extracted. If only the adjusted results are available, the adjusted results will be extracted, and they will be specified as the adjusted estimates.[36] If the data is presented only in graphs, we will use software such as the GetData Graph Digitizer (http://www.getdata-graph-digitizer.com/) or similar software to extract data. Any disagreement will be resolved by discussion.

Bias risk

The risk of bias of included RCTs will be evaluated according to 'Risk of bias' tool outlined in the Cochrane handbook, which include the following domains: random sequence generation (per study), allocation concealment (per study), blinding of participants and personnel (per outcome), blinding of outcome assessment (per outcome), incomplete outcome data (per outcome), selective reporting and other bias (per study). We will classify each domain as 'low',

'high' or 'uncertain' risk of bias for each included study.[37] Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer (J-H T) if needed.

Quality of evidence

Two authors (YZ and H-M F) will independently evaluate and present the quality of the evidence for each outcome using Grades of Recommendation, Assessment, Development and Evaluation (GRADE), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias.[38-39] Quality of evidence can be graded into four levels: high, moderate, low, and very low quality. The initial confidence level for each RCT will be set as high but will be rated down based on evaluations of the five domains. If there are any disagreements, we will consult a third author (J-H T). We will follow the approach suggested by Brignardello and colleagues to evaluate confidence in evidence from a network meta-analysis.[40-42]

Data synthesis

The assumption of transitivity and geometry of the networks

Considering the transitivity and homogeneity, we will divide all the evidence included into two categories. The RCTs that randomized patients at onset of CCRT will be analyzed in an NMA (Category 1), and the RCTs that randomized consolidation treatments only to patients who did not progress after CCRT will be combined and analyzed in another NMA (Category 2). We will assess transitivity by comparing the distribution of the effect modifiers across the different comparisons. All information regarding patient and study characteristics will be presented. A network plot will be generated using STATA 14.2 (Stata Corporation, College Station, USA) to present the geometry of the network of treatment comparisons across trials and assess the

feasibility of the NMA. If any trials are not connected with the network plot consisting of other trials, these will be excluded from NMA, and the results of these trials will just be described. Nodes will indicate the different consolidation treatments with/without CCRTs included in this review. The size of the nodes and thickness of the edges will be related to sample sizes of interventions and number of included trials, respectively.[43-44]

Statistical analysis

For each outcome, we will calculate the summary estimates of treatment effects with 95% CIs. For dichotomous data (i.e., tumor response, adverse effects), we will use the risk ratios (RRs) or odds ratios (ORs). For continuous data (i.e., HRQoL), we will calculate the mean differences (MDs) if outcome measurements in all studies are made on the same scale. When studies used different scales, we will use the standardized mean differences (SMDs). For time-to-event variables (i.e., OS, PFS), we will use HRs. For direct comparisons, we will use Review Manager 5.4 (Review Manager 2020, the Nordic Cochrane Center, the Cochrane Collaboration) to calculate the intervention effect. For NMA, a Bayesian NMA using the Markov chain Monte Carlo method will be performed using WinBUGS V.1.4.3 (MRC Biostatistics Unit, Cambridge, UK). We will use a hierarchical Bayesian model using three different initial values and will set 100,000 iterations after a burn-in of 50,000 for each chain. We will check for convergence visually (i.e. whether the values in different chains mix very well by visualisation). We will set vague or flat priors, $N(0, 100^2)$, for trials baselines and treatment effect priors. We will run both random-effects model and fixed-effects model according to guidance from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents.[45] We will select the model with the lower value of deviance information criterion (DIC) and the

value of residual deviance which is closer to data points to explain our results. We will calculate the probability of each treatment at each possible rank and estimate the surface under the cumulative ranking curve (SUCRA).[46] We will assess inconsistency between direct and indirect sources of evidence. We will fit both inconsistency model and consistency model. We will also complete node splitting method to explore local inconsistency.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the important clinical characteristics and methodological differences of included trials. Statistical heterogeneity will be assessed by P value ($<$ 0.10) from the Chi^2 test and the I^2 index. We will consider the P value < 0.10, and/or the value of I^2 statistic $> 50\%$ to indicate substantial statistical heterogeneity. Heterogeneity parameter τ derived from the network meta-analysis can also be used to evaluate heterogeneity. For direct comparisons, if there is no heterogeneity, a fixed-effects model will be used for meta-analysis; otherwise, a random-effects model will be adopted.

Dealing with missing data

If important data are not reported, we will make efforts to contact the study authors to obtain detailed information. We will use intention-to-treat (ITT) data whenever possible. Otherwise, we will use the data available to us, but the potential impact of them will be addressed in the assessment of risk of bias. If we cannot get the reply from authors, the data will be verified from other trials in the network or from other published meta-analyses.[47-48]

Measures for publication bias

Publication bias will be examined with the funnel plot method if at least 10 studies are included for any outcome. Small-study effects for the NMA will be assessed by constructing a comparison-adjusted funnel plot taking into account different comparisons. In the absence of small study effects, the comparison-adjusted funnel plot should be symmetric around the zero line.[49]

Subgroup analyses and sensitivity analyses

We will perform subgroup analyses. Besides, we will also complete network meta-regression to explore statistical heterogeneity across trials and inconsistency if at least 10 studies are included. We will focus on following possible effect modifiers: histology; PET-CT scan staging (Yes versus No); stage of disease; ECOG (0 versus ≥1); expression of PD-L1; types and statuses of driver genes; doses and regimens of radiotherapy. In addition, if there are identical treatment regimens except different doses or densities of treatment drugs, we will also complete subgroup analyses to investigate the influence of doses and densities of treatments, for example, divide the treatments into high doses versus low doses, high density regimens versus low density regimens (e.g., ≤q21d versus >q21d). We will execute sensitivity analyses to examine the robustness of the review findings through excluding unpublished studies, excluding lower quality studies and comparing the results of the random-effects model and the fixed-effect model.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

DISCUSSION

CCRT is a superior option and the standard care for inoperable LA- NSCLC compared with radiotherapy alone and sequential chemoradiotherapy. Consolidation therapy is a further attempt to control distant metastasis, but there are no conclusive answers yet about the effectiveness of this approach. In addition, with advances in technology, new agents (such as molecular-targeted therapy and immunotherapy) provide more treatment options. Although using durvalumab as consolidation therapy after CCRT for the treatment of unresectable LA-NSCLC is recommended in the NCCN guidelines, no studies have compared the effectiveness of all types of consolidation therapy. In addition, different CCRT regimens are used, and whether an optimal combination of CCRT and consolidation treatment exists is inconclusive. We designed this systematic review and NMA to evaluate the effects of different consolidation treatments with or without CCRTs for LA-NSCLC by synthesizing all current evidence. This NMA will combine both direct and indirect evidence via a thorough search strategy, prespecified data extraction form, and statistical methods with a Bayesian approach. The result of this NMA will provide valuable information on inoperable LA-NSCLC therapeutic options for clinicians and health practitioners.

Contributors YZ, JH-T participated in the conception and design of the study, including search strategy development. YZ, QY, BL and KH-Y tested the feasibility of the study. YZ, HM-F wrote the manuscript. YZ, LG, JH-T participated in the methodology. CW, JK-W revised the manuscript. All the authors critically reviewed this manuscript and approved the final version.

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Competing interests None declared.

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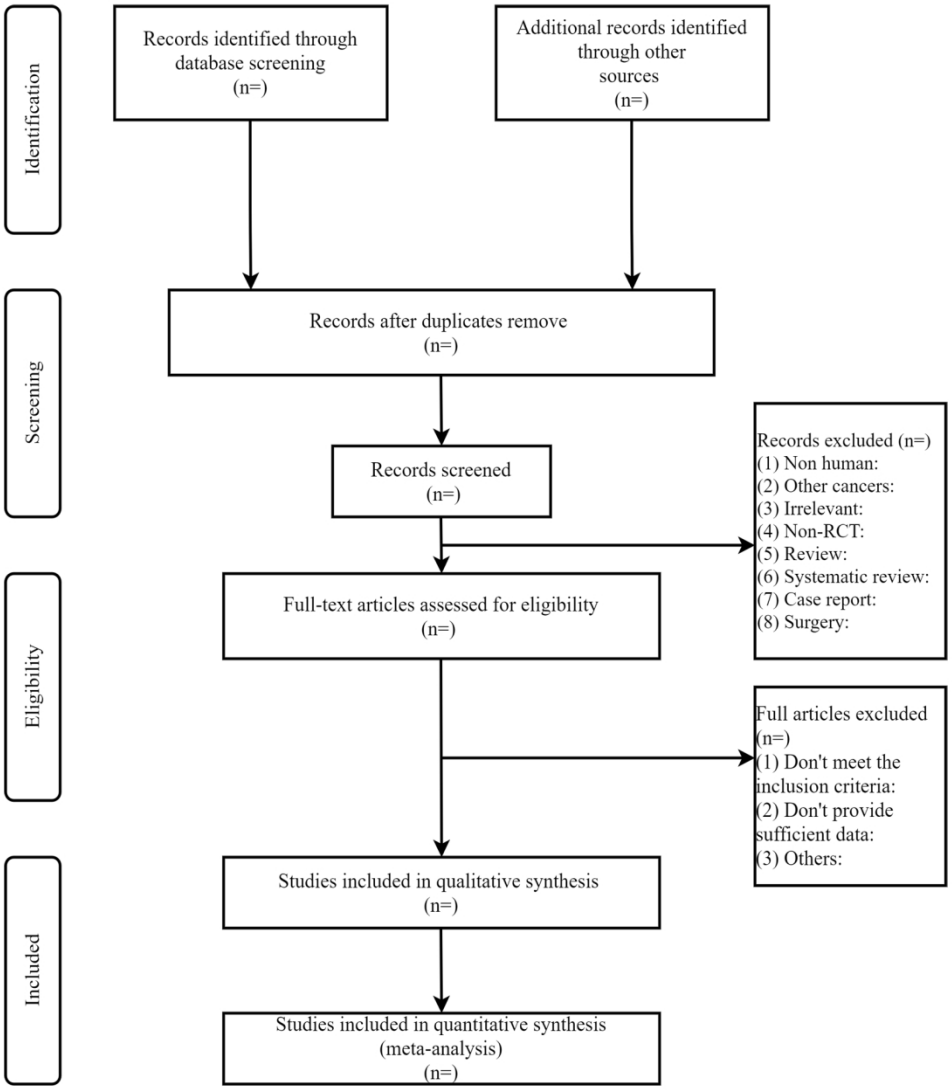

Figure 1. Flow diagram of study selection process

Medline search strategy:

Search	Query
#1	"Lung Neoplasms"[MeSH Terms]
#2	"carcinoma, non small cell lung"[MeSH Terms]
#3	(((((((NSCLC[Title/Abstract]) OR (lung cancer*[Title/Abstract])) OR (lung carcinom*[Title/Abstract])) OR (lung neoplasm*[Title/Abstract])) OR (lung tumor*[Title/Abstract])) OR (lung tumour*[Title/Abstract])) OR (non small cell*[Title/Abstract])) OR (nonsmall cell*[Title/Abstract])
#4	#1 OR #2 OR #3
#5	"Chemoradiotherapy"[MeSH Terms]
#6	((chemoradiotherap*[Title/Abstract]) OR (radiochemotherap*[Title/Abstract])) OR (CCRT[Title/Abstract])
#7	#5 OR #6
#8	"Radiotherapy"[MeSH Terms]
#9	((radiotherap*[Title/Abstract]) OR (radiation therap*[Title/Abstract])) OR (radiation treatment*[Title/Abstract])
#10	#8 OR #9
#11	("Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Antineoplastic Agents"[Mesh] OR "Chemotherapy, Adjuvant"[Mesh] OR "Induction Chemotherapy"[Mesh]) OR "Combined Modality Therapy"[Mesh]
#12	"chemotherap*"[Title/Abstract]
#13	#11 OR #12
#14	#10 AND #13
#15	#7 OR #14
#16	"Consolidation Chemotherapy"[MeSH Terms]
#17	"Maintenance Chemotherapy"[MeSH Terms]
#18	((((prolonged[Title/Abstract]) OR (duration[Title/Abstract])) OR (continu*[Title/Abstract])) OR (consolidation[Title/Abstract])) OR (maintenance[Title/Abstract])
#19	#16 OR #17 OR #18
#20	"Randomized Controlled Trial"[Publication Type]
#21	((((randomized[Title/Abstract]) OR (placebo[Title/Abstract])) OR (random*[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])
#22	#20 OR #21
#23	#4 AND #15 AND #19 AND #22

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A It is a new study
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A No funder
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A No funder
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-9
Information	#9	Describe all intended information sources (such as electronic	8-9

sources		databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9 supplemental file 1
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9-10
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	10-11
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	10-11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7-8
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the	11

		outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12-13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-14
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11-12